

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

TANAKA, et al.

Application No.: New application

Filed: Concurrently herewith

Attorney Dkt. No.: 107380-00005

For: NEW IMAGING AGENTS, PRECURSORS THEREOF AND METHODS OF
MANUFACTURE

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

June 4, 2001

Sir:

Prior to initial examination of the application, please amend the above-identified application as follows:

IN THE SPECIFICATION:

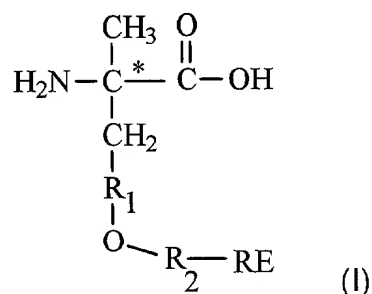
Page 1, paragraph 3, please amend as follows:

[0003] Generally speaking, PET uses radio-compounds labeled with the positron-emitters such as ^{18}F , ^{11}C , ^{13}N and ^{15}O , SPECT uses radio compounds labeled with the single-photon-emitters such as ^{18}F , ^{11}C , ^{13}N and ^{15}O , although ^{75}Br and ^{124}I can

also be used. SPECT, on the other hand, generally uses radionuclides that have more neutrons than protons, such as ^{67}Ga , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , ^{126}I , ^{131}I and ^{201}Tl .

Page 3, paragraph 10, please amend as follows:

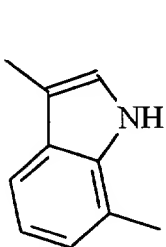
[0010] The present invention includes compounds of formula (I), or pharmaceutically acceptable salts thereof:



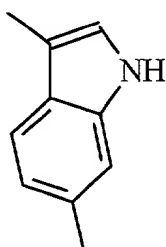
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

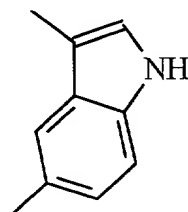
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



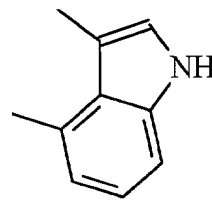
(a),



(b),



(c),



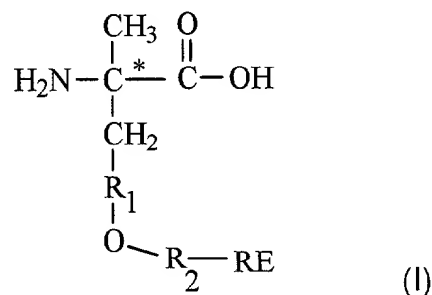
(d);

R_2 is $\text{C}_1\text{-C}_7$ alkyl; and

RE is selected from the group consisting of ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{67}Ga , ^{75}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , ^{126}I , ^{131}I and ^{201}Tl , preferably ^{123}I , ^{125}I and ^{18}F .

Page 5, paragraph 15, please amend as follows:

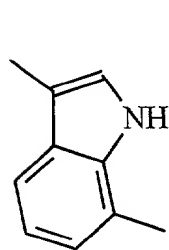
[0015] In this invention, compounds of formula I have been developed:



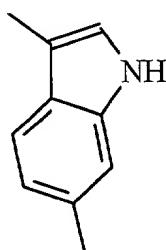
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

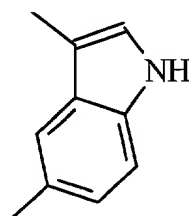
R₁ is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



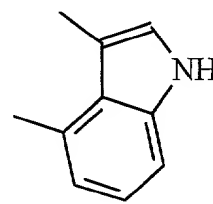
(a),



(b),



(c),



(d);

R₂ is C₁-C₇ alkyl; and

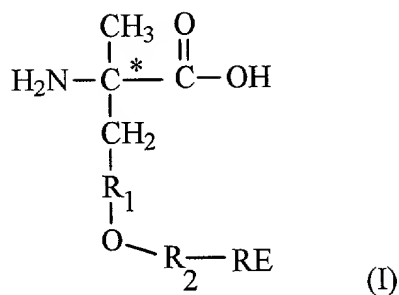
RE is selected from the group consisting of ¹¹C, ¹³N, ¹⁵O, ¹⁸F, ⁶⁷Ga, ⁷⁵Br, ⁷⁷Br, ¹²³I, ¹²⁴I, ¹²⁵I, ¹²⁶I, ¹³¹I and ²⁰¹Tl, preferably ¹²³I, ¹²⁵I, and ¹⁸F.

IN THE CLAIMS:

Please amend the claims as follows:

1. (Once Amended)
acceptable salt thereof:

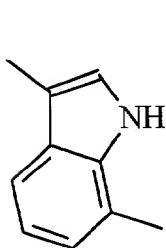
A compound of formula (I), or a pharmaceutically



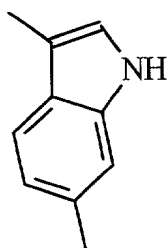
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

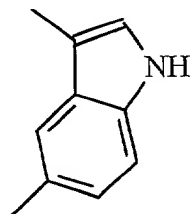
R₁ is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



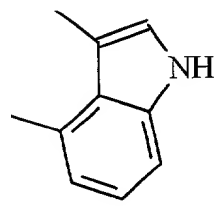
(a),



(b),



(c),

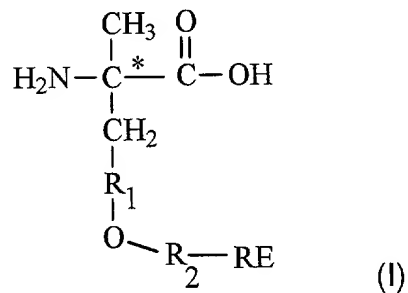


(d);

R₂ is C₁-C₇ alkyl; and

RE is selected from the group consisting of ¹²³I, ¹²⁵I and ¹⁸F.

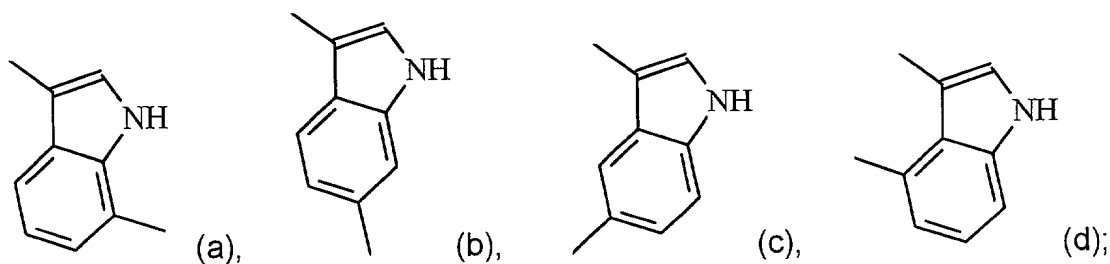
34. (Once Amended) A method of synthesizing a compound of formula (I):



wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

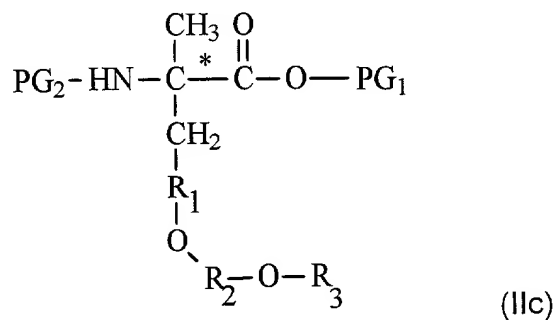
R₁ is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



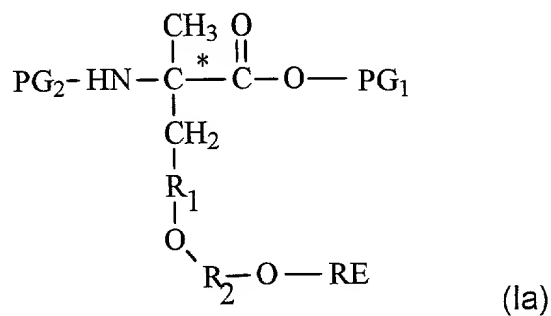
R₂ is C₁-C₇ alkyl, and

RE is selected from the group consisting of ¹²³I, ¹²⁵I and ¹⁸F,
the process comprising the following steps:

(1) reacting a compound of formula (IIc):



wherein R_1 and R_2 are the same as above, R_3 is a leaving group, PG_1 is a carboxyl protecting group and PG_2 is an amino protecting group, with a salt of RE, wherein RE is the same as above, to produce a compound of formula (Ia):

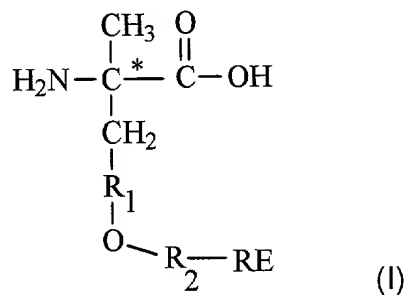


wherein R_1 , R_2 , RE, PG_1 and PG_2 are the same as above; and

(2) removing the protecting groups.

38. A method of imaging a tumor in a patient using positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging, the method comprising

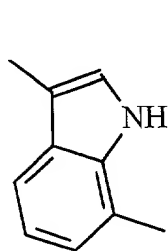
administering to the patient a tumor imaging effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof:



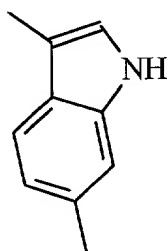
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture,

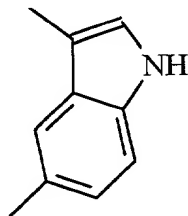
R₁ is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



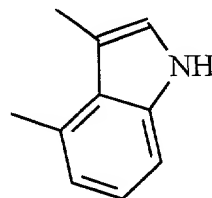
(a),



(b),



(c),



(d),

R₂ is C₁-C₇ alkyl, and


RE is selected from the group consisting of ¹²³I, ¹²⁵I and ¹⁸F; and imaging the tumor using PET or SPECT imaging.

REMARKS

Please charge any fee deficiency or credit any overpayment to Deposit Account

No. 01-2300.

Respectfully submitted,


Richard J. Berman
Registration No. 39,107

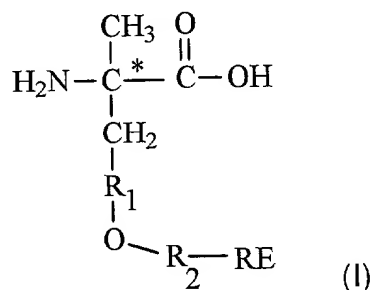
ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 Connecticut Avenue, N.W.,
Suite 600
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810

RJB/ccd

MARKED UP COPY OF SPECIFICATION

[0003] Generally speaking, PET uses Radio-compounds labeled with the positron-emitters such as ^{18}F , ^{11}C , ^{13}N and ^{15}O , SPECT uses radio compounds labeled with the single-photon-emitters [radionuclides that have fewer neutrons than protons, such as ^{18}F , ^{11}C , ^{13}N and ^{15}O , although ^{75}Br and ^{124}I can also be used. SPECT, on the other hand, generally uses radionuclides that have more neutrons than protons,] such as ^{67}Ga , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , ^{126}I , ^{131}I and ^{201}Tl .

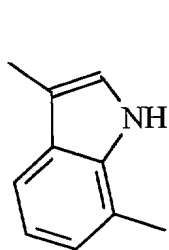
[0010] The present invention includes compounds of formula (I), or pharmaceutically acceptable salts thereof:



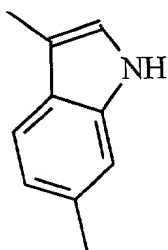
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

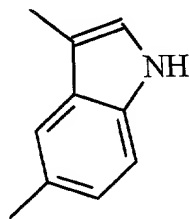
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



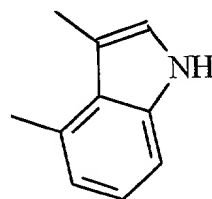
(a),



(b),



(c),

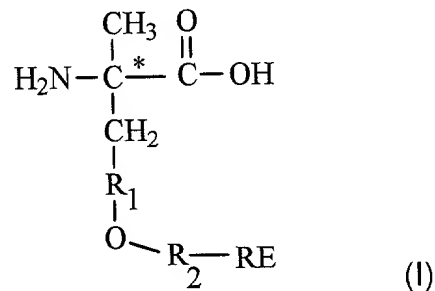


(d);

R_2 is $\text{C}_1\text{-C}_7$ alkyl; and

RE is selected from the group consisting of ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{67}Ga , ^{75}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , ^{126}I , ^{131}I and ^{201}Tl , preferably [^{75}Br , ^{124}I] ^{123}I , ^{125}I [or] and ^{18}F .

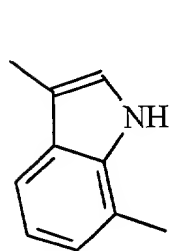
[0015] In this invention, compounds of formula I have been developed:



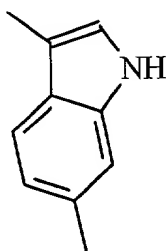
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

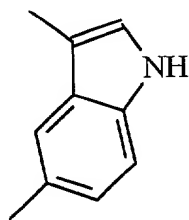
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



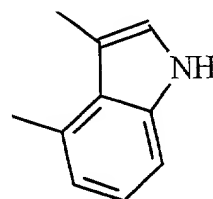
(a),



(b),



(c),



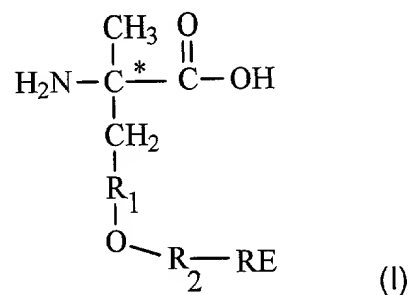
(d);

R_2 is C_1 - C_7 alkyl; and

RE is selected from the group consisting of ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{67}Ga , ^{75}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I , ^{126}I , ^{131}I and ^{201}Tl , preferably [^{75}Br , ^{124}I] ^{123}I , ^{125}I [or] and ^{18}F .

MARKED UP COPY OF CLAIMS

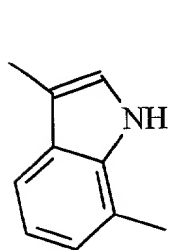
1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



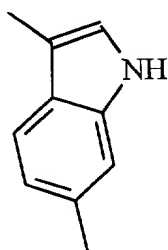
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

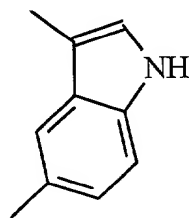
R₁ is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



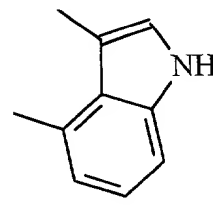
(a),



(b),



(c),

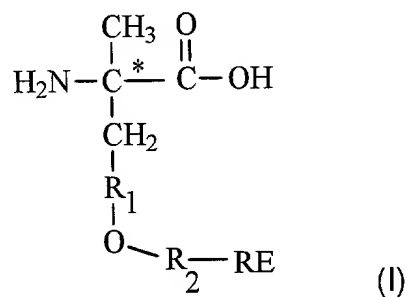


(d);

R₂ is C₁-C₇ alkyl; and

RE is selected from the group consisting of [⁷⁵Br, ¹²⁴I], ¹²³I, ¹²⁵I and ¹⁸F.

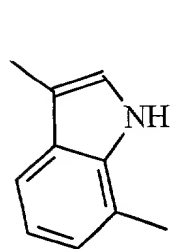
34. A method of synthesizing a compound of formula (I):



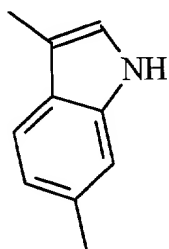
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

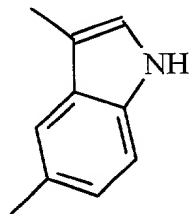
R₁ is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



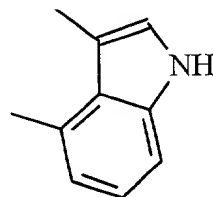
(a),



(b),



(c),



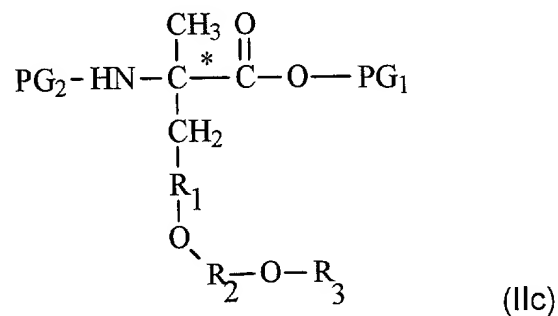
(d);

R₂ is C₁-C₇ alkyl, and

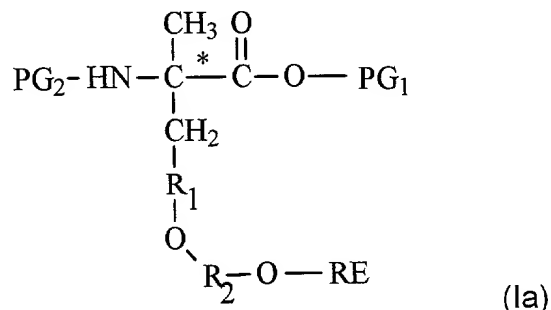
RE is selected from the group consisting of [⁷⁵Br, ¹²⁴I] ¹²³I, ¹²⁵I and ¹⁸F,

the process comprising the following steps:

(1) reacting a compound of formula (IIc):



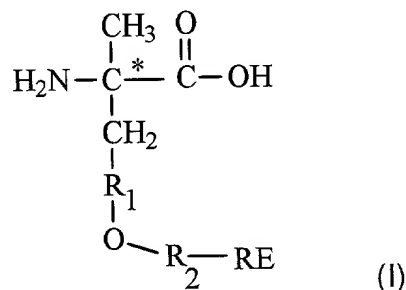
wherein R_1 and R_2 are the same as above, R_3 is a leaving group, PG_1 is a carboxyl protecting group and PG_2 is an amino protecting group, with a salt of RE, wherein RE is the same as above, to produce a compound of formula (Ia):



wherein R_1 , R_2 , RE, PG_1 and PG_2 are the same as above; and
 (2) removing the protecting groups.

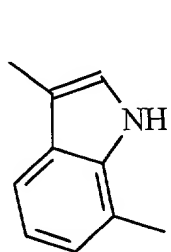
38. A method of imaging a tumor in a patient using positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging, the method comprising

administering to the patient a tumor imaging effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof:

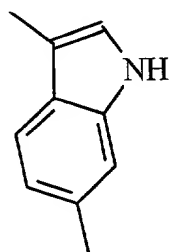


wherein
 the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture,

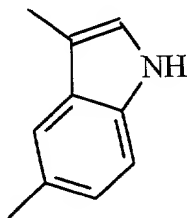
R₁ is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



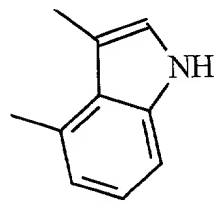
(a),



(b),



(c),



(d),

R₂ is C₁-C₇ alkyl, and

RE is selected from the group consisting of [⁷⁵Br, ¹²⁴I] ¹²³I, ¹²⁵I and ¹⁸F; and imaging the tumor using PET or SPECT imaging.